UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/367,950	08/18/1999	TOMMY EKSTROM	06275/188001	4952

26161 7590 06/16/2006

FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
KIM, JENNIFER M	
ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/367,950
Filing Date: August 18, 1999
Appellant(s): EKSTROM, TOMMY

Janis K. Fraser
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 3, 2006 appealing from the Office action mailed September 21, 2005 and the Advisory Action dated December 14, 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 93/11773	CARLING et al.	06-1993
5,795,564	ABERG et al.	08-1998

Ryrfeldt et al. "Pulmonary disposition of the potent glucocorticoids developed for the local treatment of respiratory disorders such as bronchial asthma and allergic rhinitis". Biochem. Pharmacol., 1989, 38(1), 17-22.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 13, 35, 36 and 42 are rejected under 35 U.S.C. 112, first paragraph.

Claims 13-15, 17, 18, 20-36, 38, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling of record.

Claim 16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al. of record as applied to claims 13-15, 17, 18, 20-36, 38, 42 and 43 above, and further in view of Aberg et al. (U.S.Patent 5,795,564) and Ryrfeldt et al. of record.

Claim Rejections - 35 USC § 112

1. Claims 13, 35, 36 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment of an acute episode of asthma", does not reasonably provide enablement for the "prevention of an acute episode of asthma". The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

2. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method of treating or **preventing** an acute episode of asthma in a patient with an effective amount of a composition comprising formoterol and budesonide that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a **preventive** measure, when the patient experiences an increase in symptoms of an acute episode of asthma. The nature of the invention is extremely complex in that it encompasses the actual prevention of an acute episode of asthma such that the subject treated with above composition does not contract an acute episode of asthma.

Breath of the Claims: The complex of nature of the claims
Greatly exacerbated by breath of the claims. The claims encompass prevention of a complex cell autoimmune disorder in humans which has potentially many different causes (i.e. many different allergen or combination of allergens). Each

of which may or may not be addressed by the administration of the claimed composition.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed composition to a subject in order to actually prevent an acute episode of asthma is minimal. All of the guidance provided by the specification is directed towards treatment rather than prevention of an acute episode of asthma.

Working Examples: All of the working examples provided by the specification are directed toward the treatment rather than prevention of an acute episode of asthma.

State of the Art: While the state of the art is relatively high with regard to treatment of an acute episode (i.e. acute asthmatic attack), the state of the art with regard to prevention of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a composition similar to the claimed compounds was administered to a subject to prevent development of an acute episode of asthma.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual prevention of an acute episode of asthma in a human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of prevention of an acute episode of asthma.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of

appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for **prevention** of an acute episode of asthma. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard prevention of an acute episode of asthma with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding prevention of an acute episode of asthma with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of an acute episode of asthma in a subject by administration of the claimed composition.

Therefore, a method of **preventing** an acute episode of asthma in a patient in need thereof administering composition comprising formoterol and budesonide that the patient is instructed to inhale the composition on demand, as determined by the patient based on the patient's symptoms, as a treatment and a **preventive** measure, when the

patient experiences an increase in symptoms of an acute episode of asthma is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

1. Claims 13-15, 17, 18, 20-36, 38, 42 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling of record.

Carling et al. on page 6, lines 5-30, teach the suitable daily asthmatic dose of formoterol fumarate dihydrate as required by claim 15 and budesonide within Applicant's daily dosage of "on demand" (twice a day) and the dosages strongly depends on the patient (age, weight etc.), severity of disease (mild, moderate, severe asthma etc..).

Carling et al. on pages 7-9 exemplify amounts of active agents per dose of inhalation, which calculate up to 8 inhalation per day without going over the maximum daily dosage.

Carling teaches at page 8-14, page 3, line 35 through page 4, line 10, lines 30-35, page 6, lines 5-30, and page 7, lines 1-5, teach a composition comprising Applicant's active agents use for treating respiratory disorder such as asthma set forth in claims 13-15, 17-18, 20-21, and 23.

Carling et al. at page 4, lines 3-10, also teach that the combination of formoterol and budesonide has not only a greater efficiency and duration of bronchodilator action but also a rapid onset of action.

The difference between Carling et al. and Applicant's invention is instructing a patient to inhale, on demand, as determined by the patient based on the patient's symptoms, to provide short-term symptomatic relief of acute asthmatic symptoms set forth in claims 13 and 36, instructing patient to inhale additional doses as needed if he experiences asthma including acute asthmatic episode, a specific carrier set forth in claim 24, the molar ratio of active agents set forth in claim 14, and the particle size set forth in claim 22.

However, to instruct the patient to inhale, on demand, as determined by the patient's symptoms in acute asthmatic episode is obvious since Carling et al. teach that the dosages strongly depends on the severity of disease (mild, moderate, severe asthma) and the suitable daily dosage is up to 8 inhalation. One of ordinary skill in the art would be motivated to instruct those patient with severe asthma or acute asthmatic attack to use the Carling's composition as needed bases up to 8 inhalations as suggested by Carling et al. that the dosages strongly depends on the severity of disease and to achieve maximum benefit of daily dosage recommended by Carling et al. It is noted that combination of formoterol with budesonide is well known to be beneficial for the treatment of asthma as taught by Carling et al. Moreover, if that patient experiencing acute asthmatic attack even with ongoing twice a day dosing regimen, he still can safely inhale additional 6 inhalations without going over the maximum suitable daily dosage in general asthmatic condition taught by Carling et al. to achieve its known therapeutic relief from asthmatic attack. The skilled artisan would have been motivated to instruct the patient to use Carling's composition as needed

bases up to 8 inhalations a day with reasonable expectation of successfully achieving maximum benefit in treatment of any severity condition of asthma in general including acute asthmatic condition.

The molar ratio of active agents to be used set forth in claim 14, the selection of carrier set forth in claims 23 and 24, and the particle size of active agents set forth in claim 22, are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations.

Claim 16 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carling et al. of record as applied to claims 13-15, 17, 18, 20-36, 38, 42 and 43 above, and further in view of Aberg et al. (U.S.Patent 5,795,564) and Ryrfeldt et al. of record.

Carling et al. as applied as before.

Carling et al. do teach the isomer of formoterol set forth in claim 16 and the specified epimer of budesonide set forth in claim 19.

Aberg et al. teach (R, R) isomer of formoterol as required by claim 16 is a potent bronchodilator with reduced adverse effects in treatment of asthma. (abstract, column, 1, lines 25-35).

Ryrfeldt et al. teach that 22R epimer of budesonide is more potent in the treatment of bronchial asthma than 22S epimer.

However, it would have been obvious to one of ordinary skill in the art to employ (R, R) enantiomer of formoterol and 22 R epimer of budesonide in view of Aberg et al.

and Ryrfeldt et al. because both of the references of Aberg and Ryrfeldt teach specific isomers form that possesses potent asthmatic effect of the active agents utilized in Carling reduced adverse effects in treatment of asthma. One would have been motivated to employ (R,R) isomer of formoterol and 22R epimer of budesonide in Carling's composition with reasonable expectation of successfully treating asthmatic patients with reduced adverse effects.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

(10) Response to Argument

Appellants argue after a careful consideration of all of the Wands factors (Nature of the invention, Breath of the claims, Guidance in the specification, Working Examples, State of the Art, Predictability of the Art, and the amount of experimentation Necessary) and the evidence of record in this case makes it clear that the Examiner's concern regarding enablement of the "**prevention**" aspect of the present claims are unwarranted. This is not persuasive because the first paragraph of 35 U.S.C. 112 requires that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. A number of factors are relevant to whether undue experimentation would be required to practice the claimed invention including the Wands factors. With respect to the claimed invention, the relative skill of

those in the art is quite high and weighs in favor for the **aspects** of "treatment" of asthma, however, the remaining factors of "prevention" weigh against because there is **no absolute "prevention"** of such disease. Rejected claims 13, 35, 36 and 42 is broad as it encompasses actual prevention and therapeutic administration of the combination comprising budesonide and formoterol to treat and prevent such symptoms of asthma. The amount of direction of guidance provided can only be described as minimal. According to the specification the subject being administered with the combinations are for the **treatment** of **sporadic breakthrough symptoms** (Example 5) and **having the symptoms of asthma** (Example 6). There is no evidence of record that asthma can be **absolutely prevented** by any compound. The quantity of experimentation required to practice the absolute prevention would be considerable. For this reason, analysis under the Wands factors conclude that appellant's disclosure would not enable a person of skill in the art to practice the claimed invention of **absolute "prevention" without undue experimentation.**

Appellants argue that each of the rejected claims is limited to methods in which the patient is instructed to inhale the formoterol/budesonide composition either "on demand, as determined by the patient" or "as needed" but Carling et al.'s intended dose regimen is a twice daily administration. This is not persuasive because while Carling et al. teach the twice a day dosing administration, Carling et al. also teach that the regimen also depend on the severity of the disease as well as patient's physiology. (page 6, lines 21-29). Carling et al. also provide working examples comprising amounts of active agents per doses of inhalation, which one of ordinary skill in the art could easily

calculate up to 8 inhalations per day without going over the maximum daily dosage taught by Carling et al. on page 6, lines 21-29). Therefore, it would have been obvious to one of ordinary skill in the art to instruct asthmatic patient to inhale additional doses as needed if he experiences acute asthmatic episode without going over the maximum daily dose taught by Carling et al. One of ordinary skilled in the art would be motivated to instruct the patient to administer extra dose determined by the patient's experience of symptoms not controlled by standby, maintenance dosing of twice a day in order to assist an emergency situation may arise in the asthmatic patient. One of ordinary skill in the art would be motivated to make such modification because Carling et al. teach that regiment can be differ by the severity of the asthmatic condition and broad range of effective daily dose also taught by Carling et al. Carling et al. teach the safe and effective amounts of each of the active agent that can be administered daily for the treatment of asthma. (column 6, lines 21-29). Appellants argue that the reference itself actually says nothing about the number of inhalations per administration, rather only that those inhalations should be grouped into just two administrations per day. To this response, the reference teaches the safe and effective maximum daily dosages, the reference teaches how you can formulate unit dose amounts, and finally reference teaches the regimen can be adjust to patient's severity of the condition. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the regimen according to patient's severity of condition up to maximum safe dose in order to effectively treat sporadic asthmatic symptoms when the patient experiences it in order to avoid life threatening asthmatic episodes. Appellants argue

that one of ordinary skill in the art of asthma therapy would have agreed with Appellant's interpretation of Carling et al, and not with the Examiner's interpretation and the exhibits A-F show that from a date prior to the present priority date to as late as 2003, glucocorticosteroid-containing therapeutics where routinely prescribed for fixed dosage use twice per day as maintenance therapy, with the patient forbidden to vary daily dosage outside that regimen, whether "on demand," "as needed", or for any other reason. This is not persuasive because Carling et al. teach this specific combination "formoterol and budesonide" employed in the specific disease "asthma" can be administered with the combination comprising dosage ranges that are safe and effective for the treatment and that regimen can also vary and depend of the severity of the disease. It is routine procedure for the one of ordinary skill in the art to adjust, and instruct the patient to prepare for the daily maintenance and emergency situation wherein the severity asthmatic attacks. In this case, it is clear that one of ordinary skill in the art would instruct the patient to take additional dosage within the maximum dosages taught by Carling et al. for the specific combination therapy to cover the emergency asthmatic attacks in order to avoid life threatening situation because the daily maximum dosage is taught and the adjustment of the dosage by the severity of the asthmatic condition can be made by the severity of the disease state is also taught. Appellants argue with regarding Symbicort Turbuhaler (Exhibit B) (budesonide/formoterol combination) that there is no suggestion anywhere in the document that the patient can be in instructed to take it "as needed". However, it is the Examiner's position that one of ordinary skill in the art would take next step to optimize

patient care and to instruct the patient to take additional dosage in case of emergency determined by the patient because Carling et al. teach that maximum effective daily dosage of the combination which is workable by severity of patient's asthmatic symptoms. It is in caregiver's interest to prepare the patient for the emergency when there is no medical personals available, and Carling et al. teach the maximum daily dosage that is effective and safe for the treatment of asthma. Therefore, one of ordinary skill in the art would be motivated to instruct the patient to prepare for the emergency asthmatic attacks determined by the patient as needed to control asthmatic attack by additional dosing without going over the maximum until medical help arrives, in case emergency situation arrases. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Sreenivassan Padmanabhan
Supervisory Examiner
Art Unit 1617

Conferees:

Jennifer Kim
Patent Examiner
Art unit 1617.

JOHANN RICHTER
SUPERVISORY PATENT EXAMINER
GROUP 1600